REMARKS

Pending Claims

Prior to the entry of the claim amendments, Claims 1, 2, 5, 8, 11, 12, 16 and 22-27 are pending. Claims 1, 2, 26, and 27 are directed to an in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell. Claim 5 is directed to a transdifferentiated cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell. Claims 8, 16, 22, 23, and 24 are directed to a transdifferentiated cell by the process of Claim 1. Claims 11 and 12 are directed to a kit for converting, in vitro, epidermal basal cells into cells having one or more morphological, physiological and/or immunological feature(s) of a glial cell. Claim 25 is directed to an in vitro cell culture derived from the transdifferentiated cell of Claim 8.

Contrary to the Office Action Summary attached to the Office Action issued June 3, 2003, Claim 8 is still pending in the above-captioned application.

The Office Action and Applicant's Amendment and Response

Drawings. The Examiner noted that the drawings filed April 7, 2000 remain objected to as stated in the previous Official action mailed 11/20/2002, where a PTO-948 was provided, since the required corrections have not been made. In response, Applicant herewith submits formal renderings of photographs submitted as drawings pursuant to 37 C.F.R. § 1.84(b)(1).

Specification. Applicant's amendment at page 1, line 4, is merely to update the continuing data concerning parent application Serial No. 09/234,332, filed on January 20, 1999, which issued as U.S. Patent No. 6,087,168, on July 11, 2000.

Claims. The amendment in the preamble of Claim 1, line 2, deleting the superfluous "(s)" at the end of "features~~(s)~~" is merely a refining amendment.

Applicant's amendments at the ends of Claims 1 and 5, "or ~~a combination~~ expressing both of these." are merely for greater clarity, and do not change the intended scope of these

claims.

The amendments to Claim 2, line 5 and Claim 5, line 5, inserting the word "sequence" after the word "DNA" are merely for greater clarity, and do not change the intended scope of these claims.

The amendment to Claim 11, (A), inserting the word "selected" into the phrase "transcription factor selected from the group consisting of", is merely a refining amendment.

Applicant has amended the preamble of Claim 23 to recite "The transdifferentiated cell of Claim 8", which refining amendment is merely to make the preamble of Claim 23 (dependent from Claim 8) consistent with those of Claim 8 and its other dependent Claims 16, 22, and 24, and does not change the intended scope of Claim 23.

Applicant has added new Claims 28-46.

Support for new Claim 28 is found in the specification, e.g., in Claim 1 as originally filed.

Support for new Claim 29 is found in the specification, e.g., in Claim 2 as originally filed.

Support for new Claim 30 is found in the specification, e.g., in Claim 5 as originally filed.

Support for new Claim 31 is found in the specification, e.g., in Claim 8 as originally filed.

Support for new Claim 32 is found in the specification, e.g., in Claim 11 as originally filed.

Support for new Claim 33 is found in the specification, e.g., in Claim 12 as originally filed.

Support for new Claim 34 is found in the specification, e.g., in Claim 16 as originally filed.

Support for new Claim 35 is found in the specification, e.g., in Claim 22 as originally filed.

Support for new Claim 36 is found in the specification, e.g., in Claim 23 as originally

filed.

Support for new Claim 37 is found in the specification, e.g., in Claim 24 as originally filed.

Support for new Claim 38 is found in the specification, e.g., in Claim 25 as originally filed.

Support for new Claim 39 is found in the specification, e.g., in Claim 26 as originally filed.

Support for new Claim 40 is found in the specification, e.g., in Claim 27 as originally filed.

Support for new Claim 41 is found in the specification, e.g., in Claim 1 as originally filed.

Support for new Claim 42 is found in the specification, e.g., in Claim 8 as originally filed.

Support for new Claim 43 is found in the specification, e.g., in Claim 5 as originally filed.

Support for new Claim 44 is found in the specification, e.g., in Claim 1 as originally filed.

Support for new Claim 45 is found in the specification, e.g., in Claim 1 as originally filed.

Support for new Claim 46 is found in the specification, e.g., in Claim 11 as originally filed.

Additional claim amendments are described in detail hereinbelow.

No new matter is added by any amendment herein.

The Examiner stated that "Claims 1, 2, 5, 8, 11, 12, 16, 22-27 are free of the prior art since the prior art did not teach nor fairly suggest the claimed step of use of antisense to MSX1 and HES1 found in each of the instant method and composition claims." (Office Action, at page 13, Item 5).

The Examiner stated that the specification is "enabling for using primary cells (with differentiated cells removed as in Example 1, page 25 of the specification) from human adult skin for transdifferentiation steps including administration of the human MSX1 (instant SEQ ID NOS: 13 and 14) and human HES1 antisense (instant SEQ ID NOS: 15 and 16) for making transdifferentiated cells having they physiological and/or immunological feature of a glial cell wherein said feature is expression of a marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4, or a combination of those."

However, no claims were allowed.

The Examiner stated the following reasons for rejection of the claims, under **35 U.S.C. § 112, first paragraph**.

(1) Claims 1, 2, 5, 8, 11, 12, 16 and 22-27 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner based the rejection on the assertion, *inter alia*, that:

> **...Claims 1-2, 5, 8 11-2, 16 and 22-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.**
>
> **The claims are now rejected over the breath of antisense to "a segment of a human MSX1 gene and/or human HES1 gene, or homologous non-human counterpart of either of these ... sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product".**
>
> **The specification as filed taught that MSX1 is an immediate early response gene involved in epidermal induction and inhibition of neuronal differentiation (page 3, lines 9-19); that HES1 is the hairy and enhancer of split homolog-1 (page 4, lines 21-31). The specification teaches on pages 13-14 the antisense to human MSX1 of SEQ ID NOS: 13 and 14 and the antisense to human HES1 of SEQ ID NOS:15 and 16. The GenBank Accession numbers are taught on page 14 of the human, Ambystoma mexicanum and chicken MSX1 gene and the human, rat, mouse, newt, yeast (Saccharomyces pombe and Saccharomyces cerevisiae) genes.**

While the claims are considered to describe instant SEQ ID NOS:13-16 as the antisense to human MSX1 and HES1 for making the claimed transdifferentiated cells, these sequences are not considered to represent the breath of claimed "segment of a human MSX1 gene and/or human HES1 gene, of homologous non-human counterpart of either of these ... sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product"...

... While the specification as filed teaches the Genbank sequences of human and other MSX1 and HES1 genes as summarized above, this teaching is not considered sufficient to describe the claimed genus of any non-human homologous counterpart as claimed. In order to design an antisense to a gene, the sequence of the gene much be known. The examples in the specification are not considered representative of antisense to any MSX1 or HES1 gene from any species since the examples in the specification are drawn only to human genes. Furthermore, it is not clear how antisense to any non-human homologous counterpart of MSX1 or HES1 would have a correlated function to allow for transdifferentiation of any type of epidermal basal cell into a cell expressing GFAP and/or O4. Absent further specific guidance by way of sequence structure, one of skill in the art would have recognized that applicant was in possession of a representative number of species of the breath of claimed MSX1 and/or HES1 genes from the genus of species claimed...

... The claims are now rejected over the breath of antisense to "a segment of a human MSX1 gene and/or human HES1 gene, or homologous non-human counterpart of either of these ... sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product".

The specification as filed taught that MSX1 is an immediate early response gene involved in epidermal induction and inhibition of neuronal differentiation (page 3, lines 9-19); that HES1 is the hairy and enhancer of split homolog-1 (page 4, lines 21-31). The specification teaches on pages 13-14 the antisense to human MSX1 of SEQ ID NOS: 13 and 14 and the antisense to human HES1 of SEQ ID NOS:15 and 16. The GenBank Accession numbers are taught on page 14 of the human, Ambystoma mexicanum and chicken MSX1 gene and the human, rat, mouse, newt, yeast (Saccharomyces pombe and Saccharomyces cerevisiae) genes.

While the claims are considered to describe instant SEQ ID NOS:13-16 as the antisense to human MSX1 and HES1 for making the claimed transdifferentiated cells, these sequences are not considered to represent the breath of claimed "segment of a human MSX1 gene and/or human HES1 gene, of homologous non-human counterpart of either of these ... sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product".

For greater clarity, Applicant has amended Claims 1 and 5 to delete the recitation of "antisense oligonucleotide comprising a segment of a human MSX1 gene and/or human HES1 gene, of homologous non-human counterpart, etc." and has inserted instead "antisense oligonucleotide corresponding to a human MSX1 gene and/or human HES1 gene, or to a homologous non-human counterpart, etc." Support for these amendments is found in the specification, e.g., in Claim 11, as originally filed, and at page 14, line 6.

Further, Applicant respectfully disagrees that the specification only teaches "examples drawn to human genes." The disclosures of Applicant's specification clearly teach the functional importance in the claimed method of suppressing expression of MSX1 and/or HES1 to induce the differentiation pathway toward neuronal progenitor cells and glial cells and away from the epidermal differentiation pathway (e.g., at page 9, lines 19-29; at page 10, lines 16-21; at page 14, lines 16-18; and at page 31, lines 15-18), whether in human cells or in other non-human mammalian cells. The Examiner has acknowledged the teachings of the specification as originally filed (e.g., at page 14, lines 11-18) that provide numerous examples of non-human MSX1 and HES1 sequences available to the skilled artisan in the public GenBank database, which the skilled artisan would be able to select. These GenBank accession numbers represent examples of enabling general knowledge in the art, possessed both by the skilled artisan and Applicant, as to detailed sequence information, such that a voluminous compendium comprising numerous complete non-human sequences already available in the art need not be recited in the above-referenced application. The specification also teaches (e.g., at page 14, lines 16-29) that well known computerized genomic databases and algorithms (e.g., various BLAST software programs) enable the skilled artisan to do a search of sequence similarity, among non-human homologous counterparts of human MSX1 and HES1, in these genomics databases for antisense oligonucleotide sequences that would hybridize to the applicable MSX1 and/or HES1 gene sequence to prevent translation of functional MSX1 or HES1 proteins in the epidermal basal cells derived from humans and non-human mammals. Consequently, the conserved regions of MSX1 and HES1 genes across

species become readily apparent to the skilled artisan, who with this knowledge knows how to construct suitable antisense oligonucleotides.

Accordingly, Applicant respectfully requests the Examiner to withdraw the rejection of Claims 1, 2, 5, 8, 11, 12, 16 and 22-27 on this ground.

(2) Claims 1, 2, 5, 8, 11, 12, 16 and 22-27 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to, to make and/or use the invention. The Examiner based this rejection the basis that Applicant had not demonstrated possession of glial cells in the specification. Applicants respond to this rejection as provided above. In addition, the Examiner stated that

> **. . . the specification, while being enabling for using primary cells (with differentiated cells removed as in Example 1, page 25 of the specification) from human adult skin for transdifferentiation steps including administration of the human MSX1 (instant SEQ ID NOS: 13 and 14) and human HES1 antisense (instant SEQ ID NOS: 15 and 16) for making transdifferentiated cells having they physiological and/or immunological feature of a glial cell wherein said feature is expression of a marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4, or a combination of those, does not reasonably provide enablement for the breath of methods and transdifferentiated cells claimed from any possible epidermal basal cell, and further, using antisense to MSX 1 and HES1 form any species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. . .**
>
> **. . . The specification as filed teaches that human adult skin was cultured and transfected with pRcCMVneo vectors containing B-gal, NeuroD1, NeuroD2, hASH1, Zic1 or hMyT1 human genes. The specification teaches in example 3 the design of two antisense oligonucleotides to target human MSX1 (SEQ ID NOS: 13 and 14) and two antisense oligonucleotides to target human HES1 (SEQ ID NOS: 15 and 16). In example 4, the specification teaches the methods for detection of transdifferentiation of the epidermal cells to neural cells as immunohistochemical detection of neurofilament M, neural specific tubulin, neural specific enolase, microtubule associated protein 2, neuroflaments Mix, filial fibrillary acidic protein, and morphological criteria. The specification teaches that cells with neurites longer than three cell diameters (50 microns or longer) and expressing at least one neuronal marker were counted as neuron. Table 1 teaches the results of the transdifferentiation experiments showing that a combination of**

neurogenic transcription factor expression coupled with decrease in MSX1 and HES1 expression was most effective at establishing transdifferentiation. The specification only teaches in Table 1 a defined set of cells having some characteristic of a differentiated neuronal cell, the structure of which is not adequately described therein, and would not appear to have the instantly claimed features of a glial cell. The specification does teach on page 31, lines 13-16 that a "small percentage (around 5%) of cells also express GFAP. This is an indication that transdifferentiated cells acquire characteristics of astroglial cells, either directly or indirectly." However, no further guidance as to which type of epidermal basal cells would differentiate into cells having GFAP and/or O4 markers, have been provided in the specification. Nor has any guidance been provided as to the breath of antisense to any species of MSX and/or HES that will provide the functions claims of transdifferentiating the epidermal basal cells into cells having the GFAP and/or O4 markers. . .

. . . The level of unpredictability in the field of development of glial cells from epidermal basal cells was high. One of skill in the art could not predict whether or not cells having GFAP and/or O4 markers could be produced from epidermal basal cells in cell culture. Nor could one of skill in the art predict whether or not cells having GFAP and/or O4 markers could be made from any type of epidermal basal cells from any organism using the methods disclosed in the instant specification as filed. Absent more specific guidance in the art for which specific cell populations may be used and which antisense must be expressed in the such epidermal basal cells, one of skill in the art would necessarily practice an undue amount of experimentation to make and use the breath of claimed transdifferentiated glial cells and methods of making said cells.

Applicant has herein amended Claim 1 and Claim 26 (which depends from Claim 1), directed to "a method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological features(s) of a glial cell, comprising:

(a) culturing a proliferating primary epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject . . ."

Claim 5 has been amended herein to recite, "A transdifferentiated mammalian cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell, comprising:

a cultured primary epidermal basal cell transfected, etc. . . ."

Applicant has amended Claim 11 to recite, "A kit for converting, in vitro, primary epidermal basal cells into cells having one or more morphological, physiological and/or immunological feature(s) of a glial cell . . ."

These amendments, limiting the source of the transdifferentiated "*cells having one or more morphological, physiological and/or immunological feature(s) of a glial cell*" to cultured *primary* epidermal basal cells, is believed to overcome the basis of the Examiner's rejection, together with the amendments to Claims 1 and 5 (discussed above), concerning ". . . at least one antisense oligonucleotide corresponding to a human MSX1 gene and/or a human HES1 gene, or to a homologous non-human counterpart of either of these [thereof]." Moreover, Applicant is aware of no references that would contraindicate the fact that the claimed method, transdifferentiated cells and kits are applicable for epidermal basal cells of mammalian juveniles, as well as those of adults.

Accordingly, Applicant respectfully requests the Examiner to withdraw the rejection of Claims 1, 2, 5, 8, 11, 12, 16 and 22-27 on this ground.

CONCLUSION

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

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